Cell Metabolism
Previews

Lipotoxicity and the Development of Heart Failure: Moving from Mouse to Man

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Intracardiac lipid accumulation can cause heart failure. A study in *Journal of Clinical Investigation* (Son et al., 2010) found that cardiac-specific PPARγ overexpression caused heart failure with intracardiac triglyceride accumulation. Overexpressing PPARγ on a PPARα−/− background improved cardiac function, suggesting that specific lipid metabolites and lipid packaging determine cardiac lipotoxicity.

Over the last 40 years, there has been a leap forward in the ability to prevent heart disease through diet, physical activity, and aggressive medical management of hypertension and blood lipids (van Dam and Willett, 2009). Unfortunately, in the United States, this has been a missed opportunity, as there is a continued high rate of heart disease, largely attributable to physical inactivity, excessive energy intake, and resultant obesity. Obesity triggers hypertension, hyperlipidemia, glucose intolerance, and diabetes, which cause atherosclerosis, cardiac hypertrophy, ischemic heart disease, and ultimately heart failure (Lavie et al., 2009) (see Figure 1). It has been proposed that independent of these established risk factors, intracardiac accumulation of lipids could exert toxic effects on the myocardium that would directly cause cardiac dysfunction, cell death, and the development of heart failure (Unger, 2002; Schaffer, 2003). Investigation into this hypothesis has placed growing emphasis on understanding the role of specific fatty acyl metabolites and intracellular packaging of lipid stores as potential mediators of the toxic effects of lipids in the heart.

In a recent issue of *Journal of Clinical Investigation*, Son et al. addressed this hypothesis by altering the capacity for lipid import and oxidation and analyzing the resulting cardiac phenotype (Son et al., 2010). They observed that PPARγ overexpression in the heart caused dilated cardiomyopathy and poor survival that was associated with intracardiac triglyceride accumulation. Crossing this cardiac-specific PPARγ-overexpressing mouse with a PPARα−/− mouse increased cardiac fatty acid oxidation and lipid droplet size, which corresponded with improved cardiac contractile function and survival despite no difference in total myocardial triglyceride stores and an elevation in myocardial free fatty acid levels. The authors emphasized the potential pathogenic significance of this pattern of intracellular lipid storage, arguing that larger droplets have reduced total surface area and are likely to reflect more inert lipid storage while smaller ones may trigger harmful molecular pathways. While this cross did not result in lower diacylglycerol or ceramide levels, these mice had increased long-chain fatty acyl-CoAs and decreased acylcarnitines and various markers of cell stress. These findings add further support for the concept that neither cardiac storage of triglycerides nor oxidation of fatty acids is inherently detrimental to the heart and suggest that specific fatty acyl derivatives may be responsible for the toxic effect of lipid accumulation. Of particular interest is the relationship between accumulation of long-chain fatty acyl carnitines and poor cardiac function and survival, as these compounds are associated with effects on sarcolemmal ion channels that cause cardiac arrhythmias (Corr and Yamada, 1995), which are the main cause of death in heart failure patients.

The changes in the activity in PPARα and PPARγ induced by deletion and overexpression are extreme and thus are not comparable to the relatively subtle changes caused by diet or pharmacological agents in humans. Nevertheless, important information is gained from this work, particularly the observation that large changes in fatty acid uptake, oxidation, and storage do not predict changes in cardiac function or development of pathology, but rather activation of pathological processes is dependent on the manner in which triglyceride is stored and the changes in specific lipid metabolites. Unger and others proposed that the toxic effects of specific lipids contribute to the development and progression of heart failure through mechanisms that are independent of traditional well-established mechanisms depicted in Figure 1 (Unger, 2002; Schaffer, 2003). It is important to note that lipids synergize with toxic pathways involving glucose metabolism to injure the heart via glucolipotoxicity, and in obesity, high levels of insulin and leptin can stimulate prohypertrophic and pathologic signaling processes, which all together provide a "perfect storm" for the development of heart failure (Taegtmeyer and Stanley, 2010). Interestingly, PPARα−/− mice overexpressing cardiac PPARγ had a ~30% reduction in blood glucose. While insulin and leptin levels were not reported in these mice, it seems quite possible that the beneficial effects observed could be partially due to suppression of glucolipotoxicity and detrimental metabolic hormone signaling.

How do we apply these findings to the clinical problem of heart failure associated with obesity and type II diabetes? It is now well established that the risk for new-onset heart failure increases progressively with severity of obesity; however, once heart failure has been diagnosed, there is an "obesity paradox,"

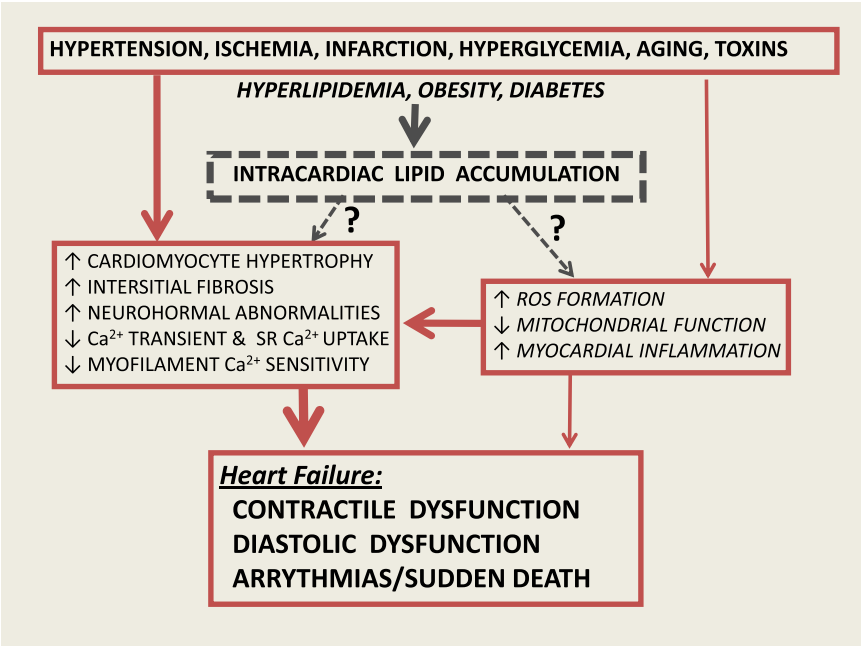

Figure 1. Potential Role of Cardiac Lipid Accumulation in the Pathophysiology of Heart Failure

Heart failure is initiated by established risk factors (maroon boxes, solid arrows) and possible effects of intracardiac lipid accumulation (dashed gray box and arrows). Chronic hypertension, ischemia, diabetes/glucose intolerance, old age, and environmental toxins like tobacco smoke trigger molecular and physiological mechanisms leading to myocardial hypertrophy, fibrosis, changes in neurohormonal regulation, tachycardia, inflammation, etc., which ultimately lead to the classic systolic and diastolic dysfunction and arrhythmias found with heart failure. Less clear is the role for myocardial lipid accumulation in these processes. Studies in cells and genetically altered mice established the possibility that various lipid moieties could trigger pathological mechanisms.

with better survival in obese heart failure patients compared to those with normal body mass (Lavie et al., 2009). Presumably this is due to differences in the etiology of heart failure between normal-weight and obese heart failure patients, with a less malignant form of heart failure with obesity. It is also possible that heart failure in some obese patients is exacerbated by accumulation of specific lipids and unidentified pathological mechanisms. It would be extremely useful to have a clinical marker for toxic lipid moieties detectable by diagnostic imaging or in cardiac biopsies. It is also important to investigate therapeutic interventions, such as low-carbohydrate/high-fat diets, which are frequently used for weight loss and maintenance and affect myocardial lipid metabolism and expression of PPAR-regulated genes (Chess and Stanley, 2008). Drugs that inhibit myocardial fatty acid oxidation, such as trimetazidine and perhexiline, show promise in small trials in heart failure patients, though the mechanism of action is not clear and the specific effects in obese heart failure patients have not been investigated (Lopaschuk et al., 2010). The findings of Son et al. provide important insight into the mechanisms by which lipid metabolism and storage can become cardiotoxic, and they illustrate the importance of moving forward to evaluate these processes in animal models of human obesity and obese heart disease patients.

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